REMARKS

Entry of the Amendment and reconsideration of the claims is respectfully requested.

Claims 52-87 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

New claims 88-109 have been added. The new claims are supported throughout the specification including at page 13, lines 3-26; page 15, lines 7-15; page 21, lines 26 to page 22, line 25; page 56, lines 20-28; and page 97, line 30 to page 98, line 4.

Interview

Applicants thank Examiner Rawlings for the interview conducted on May 23, 2005. We discussed 112, 102 and 103 rejections of record and amendments to the claims to address the rejections.

Amendment to the Specification

Applicants have amended the specification to incorporate Table 6 (also known as the Appendix, labeled herein as Attachment A). Applicants submit that when the currently pending application was filed, Table 6 was inadvertently not filed with the application. Applicants submit that this Table 6 (also known as the Appendix) was filed in the provisional application U.S. Application Serial No. 60/046,816 filed May 2, 1997 which was incorporated by reference at the time of filing of U. S. Application Ser. No.09/070,166 filed April 30, 1998. The Appendix (also known as Table 6) was entered into U.S. Application Ser. No.09/070, 166 filed April 30, 1998 by amendment to the specification. Thus, Applicants submit incorporation of this Table 6 (also known as the Appendix) does not represent new matter.

Claim Objection

Claims 82-87 were objected to because the Examiner contends the claims were constructed in an ambiguous manner. Without acquiescing to the rejection and in order to expedite prosecution, claims 82-87 have been cancelled rendering the objection moot. Applicants request withdrawal of the rejection.

35 U.S.C. § 112, Second Paragraph

Claims 52-65 were rejected under 35 USC § 112, second paragraph. The Examiner indicated that the phrase"each variable light chain..." lacks antecedent basis. Applicants have cancelled these claims and submit that the newly presented claims avoid a similar rejection. Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § First Paragraph, Written Description

Claims 52-87 were rejected because the Examiner contends the claims lack written description. While not acquiescing to the rejection and in order to expedite prosecution, claims 52-87 have been cancelled rendering the rejection with respect to these claims moot. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

The Examiner contends that members of the variable light chains differ structurally and functionally and, therefore, absent a detailed description of at least a substantial number of members of the genus of variable light chain polypeptides that have a common sequence, the claims lack written description. The Examiner also contends that the application does not describe any reduction to practice. The Examiner also contends the claims do not require that the bispecific antibody retain the binding specificity of the "parent antibodies".

The written description requirement requires that Applicants' specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula ... of the claimed subject

matter sufficient to distinguish it from other materials. Univ. of California v. Eli Lilly and Co., 43 USPQ2d 1398. 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass, such a formula is normally an adequate description of the claimed invention. Id. at 1406 (emphasis added). Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) Fed Reg. 1099, 1105 (2001); see also, In re Wertheim, 191 USPQ 90,97 (CCPA 1976). The guidelines further state that "[(The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) Fed. Reg. at 1107; 191 USPQ at 97, (emphasis added).

Applicants' claims 88-93 are directed to a method of preparing a bispecific antibody comprising a variable light chain polypeptide that has 100% amino acid sequence identity to a variable light chain specific for a first antibody and a variable light chain specific for a second antibody. Claims 94-101 are directed to method of preparing a bispecific antibody comprising a first and a second variable light chain polypeptide, wherein the first and second variable light chain polypeptides each has 3 CDRs and has at least 98% amino acid sequence identity to the other light chain variable polypeptide, and differ only at amino acid positions outside of the CDRs. Claims 102-109 are directed to a method of preparing a bispecific antibody that comprises a variable light chain, wherein the variable light chain has at least 98% amino acid sequence identity to a first antibody variable light chain domain specific for a first antigen or to a second antibody variable light chain domain specific for a second antigen or to both, wherein the variable light chain domain and the first and/or second antibody variable light chain domains differ from one another only at amino acid positions outside of CDRs.

Applicants submit that the specification as filed provides written description for the methods as claimed. Applicants direct the Examiner's attention to Figure 4 and pages 99-100. Figure 4 shows the sequence of several light chain variable domains as

described in the specification. Those light chain variable domains are from antibodies specific for different antigens and have at least 98% amino acid sequence identity to one another and only differ outside of CDRs. Applicants also direct the Examiner's attention to Table 5 and Figure 8. The Table and the Figure show that several light chain domains from antibodies specific two different antigens have at least 98%, or even 100% amino acid sequence identity. Moreover, Table 6 shows that a number of antibody clones specific for at least 11 different antigens were identified and sequenced. When the sequences of light chain variable domains were compared, at least one or more than one light chain can be identified having at least 98% amino acid sequence identity to an antibody light chain from an antibody specific for a different antigen. Thus, Applicants submit they have provided many examples of the structure of light chain variable domains.

Secondly, the Examiner contends that the specification does not provide an actual reduction to practice of method of preparing a bispecific antibody. Applicants respectfully disagree. Applicants describe the preparation of a bispecific antibody with binding specificity for Ob-R and HER3. See page 98, lines 5 to page 101, line 19.

In addition, Applicants note that the many antibody sequences are available. One of skill in the art could readily search for antibodies of different specificities that have light chain variable domain sequences that have at least 98% amino acid sequence identity to one another using publicly available databases and searching tools.

Finally, the Examiner also contends that the claims do not require that the bispecific antibody retain the binding specificity of each of the parent antibodies. Applicants respectfully disagree. The currently pending claims address the Examiner's rejection.

Based on the foregoing, Applicants respectfully request withdrawal of the rejection on this basis.

35 U.S.C. § 112, First Paragraph, Enablement

The Examiner rejected claims 52-54, 58-63, 66-71, 74-79 and 82-87 under 35 U.S.C. § 112, first paragraph. The Examiner contends that these claims are not enabled.

Applicants have cancelled claims 52-87 without prejudice or disclaimer rendering the rejection of these claims moot. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

The Examiner contends that the specification does not enable a method where the bispecific antibody does not retain the binding specificities of two antibodies comprising light chain polypeptides that share a common sequence or have at least 98% identity to those polypeptides. The Examiner contends that undue experimentation would be required because of the magnitude of number of different antigens that may be recognized by the antibody. The Examiner also contends that one of skill in the art cannot predict which light chains have a common sequence or at least 98% amino acid sequence identity to one another and differ only at positions outside of CDRs.

Applicants contend that one of skill in the art reading this specification would be able to practice methods of preparing a bispecific antibody as claimed without undue experimentation. There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Only a reasonable correlation is required.

Applicants submit that the claims as amended address at least some of the Examiner's concerns. Applicants have amended the claims to indicate that the variable light chain domain has at least 98% amino acid sequence identity or even 100% amino acid sequence identity to a variable light chain domain for a first antigen and/or a variable light chain domain specific for a second antigen. Thus, Applicants submit that the method provides bispecific antibodies that have a binding domain specific for the first antigen and a binding domain specific for the second antigen. Applicants submit that the bispecific antibodies will not need to be screened against a magnitude of antigens.

Secondly, the Examiner contends that it is not predictable which antibody light chains will have at least 98% amino acid sequence or even 100% amino acid sequence identity. Applicants submit that Applicants have shown that light chain variable domains

having at least 98% or even 100% amino acid sequence identity can be identified for almost any pairwise combination of antibodies specific for different antigens. See for example, Table 5 and Table 6. Applicants submit that they have established that such light chains are readily identified. Applicants have provided the sequences of several of antibody variable light chains in Figure 4. Moreover, any identification and/ or modification of light chains variable domains that have a sequence that is at least 98% identical is routine and will not require undue experimentation. A large amount of experimentation can be required as long as it is routine.

Applicants further submit that the specification enables the full scope of the currently pending claims. Applicants have provided several working examples and several examples of sequences of light chain variable domains that have at least 98% amino acid sequence identity. See Figure 4. In addition, Applicants have provided a working example of making a bispecific antibody specific for Ob-R and HER3. See pages 98-101 in the specification. In Tables 5 and 6, Applicants have shown that a variable light chain domain that has at least 98% amino acid sequence identity can be identified for most pairwise combinations of antigens. Applicants have provided a comparison of the sequences of antibody variable light chains in Figure 4. The knowledge of those of skill in the art about antibody structure and function is high. Applicants submit one of skill in the art reading the specification can readily practice the claimed methods.

Applicants further submit that Applicants have taught that antibodies that have different antigen specificities can be identified that have light chain variable domains that have at least 98% amino acid sequence identity to one another and only differ outside of CDRs. Applicants have provided a description and working examples of the methods of the invention. One of skill in the art can further utilize antibody sequences that are available in databases to identify antibodies with different specificities that have light chain variable domains that have at least 98% amino acid sequence identity and only differ at amino acid positions outside of CDRs.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph, rejection.

The Examiner also contends that it would be unpredictable if the antibody light chains, especially those with amino acid differences would interact with functionally different heavy chains. The Examiner contends that a single amino acid change can affect binding of the antibody and cites several references to support this contention. Applicants disagree.

The Examiner has cited several references and asserts these references would lead one of skill in the art to conclude that making any changes in the antibody sequence would destroy antibody function. Applicants disagree. The references cited by the Examiner have dates of 1987 and 1989. These references are over 15 years old. Applicants submit that the understanding of antibody structure and function has advanced considerably since that time. Moreover, in the Caldas et al. reference (2003) a change in framework residue was made in the antibody, but the antibody still bound to the antigen, but with a lower affinity. In addition, in some embodiments, the antibodies having the light chain variable domains according to the claims have been shown to bind to the antigen.

Thus, Applicants submit that one of skill in the art reading the specification would be able to practice the invention without undue experimentation. Based on the foregoing, Applicants request withdrawal of the rejection on this basis.

35 U.S.C. § 102(b)

The Examiner rejected claims 52, 55-56, 66 and 71-72 under 35 U.S.C. § 102(b) as anticipated by Mallender as evidenced by Gulliver. Applicants have cancelled claims 52-87 without prejudice or disclaimer, rendering the rejection of these claims moot. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

Applicants submit that the currently pending claims are directed to a method of making a bispecific antibody comprising a variable light chain domain wherein the variable light chain polypeptide has 100% amino acid sequence identity to a variable light chain from a first antibody specific for first antigen and to a variable light chain from a second antibody specific for a second antibody. The Mallender et al. reference

does not teach a method for making a bispecific antibody with a variable light chain as claimed. A sequence comparison of the antibody variable light chain domains of antibody 4-4-20 and antibody 4-01 shows that they have less than 98% amino acid sequence identity and amino acid differences within the CDRs (sequences provided as Attachment B). Applicants submit that based on the sequence comparison it is not accurate to deem the light chains of the bispecific antibody described in Mallendar to have at least 98 % sequence identity to one another. Thus, for at least this reason, the Mallender et al. reference does not anticipate any of the claims.

Applicants, therefore, respectfully request withdrawal of this rejection.

35 U.S.C. § 103(a)

The Examiner rejected claims 52-57, 66-68 and 71-73 under 35 U.S.C. § 103(a) as being unpatentable over Shalaby et al. as evidenced by Carter et al., in view of Zhu et al. Applicants have cancelled claims 52-87 without prejudice or disclaimer rendering the rejection of these claims moot. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

The currently pending claims 88-93 are directed to a method for producing a bispecific antibody comprising introducing into a cell a nucleic acid encoding the variable light chain domain polypeptide wherein the variable light chain polypeptide has 100% amino acid sequence identity to a first variable light chain specific for a first antigen and to a second variable light chain specific for a second antigen.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, in the least, because the references even when combined do not teach all the limitations of the claims, and there is no motivation to combine the references in the manner suggested by the Examiner.

The Shalaby et al. reference is directed to bispecific $F(ab')_2$ with one arm specific for HER2 and one arm specific for CD3. The method involves secretion from E. coli of each F(ab') followed by directed chemical coupling. The Shalaby et al. reference does not teach or suggest a method for culturing a host cell comprising one or more nucleic acids encoding the first polypeptide, the second polypeptide and the variable light chain domain polypeptide. Moreover, there is no teaching or suggestion of using a variable light chain that has at least 98% amino acid sequence identity or even 100% amino acid sequence identity. The light chains of each of the binding domains of this bispecific antibody have less than 98% amino acid sequence identity and have changes in both the framework regions and the CDRs. There is no teaching or suggestion to use a variable light chain that has at least 98% amino acid sequence identity to improve production of bispecific antibodies because in the method of Shalaby et al. it would not be necessary because each F(ab') is produced separately and then coupled together chemically. There is no mispairing of heavy and light chains when each F(ab') is produced separately.

The deficiencies of Shalaby et al. are not remedied by reference to Carter et al. or Zhu et al. The Carter et al. reference does not discuss bispecific antibodies at all. The Zhu et al. reference is directed to methods of preparing bispecific antibodies, but does not teach or suggest that a method comprising culturing a host cell comprising one or more nucleic acids encoding the antibody variable light chain polypeptide, wherein the variable light chain polypeptide has 100% amino acid sequence identity to a first antibody variable light chain polypeptide specific for a first antigen and to a second antibody variable light chain polypeptide specific for a second antigen. Thus, even when the references are combined they do not disclose all of the elements of the claimed methods.

Moreover, there would be no motivation to combine these references. The Shalaby reference indicates that the method described therein provides for efficient production. Moreover, none of the methods discuss or even suggest that a method of making a bispecific antibody comprising a common variable light chain domain. The Zhu et al. reference provides several strategies for designing multimerization domains, but nowhere teaches or suggests a method of making a bispecific antibody comprising a common variable light chain domain.

Thus, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. 103

Claims 52-85 were rejected under 35 U.S.C. 103(a) as unpatentable over Reddy et al., Vaughan et al., and Zhu et al., for reasons of record. Applicants have cancelled claims 52-87 rendering the rejection of these claims moot. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, in the least, because the references even when combined do not teach all the limitations of the claims, there is no motivation to combine the references in the manner suggested by the Examiner, and because there would be no reasonable expectation of success in doing so.

Applicants' claims 88-93 are directed to a method of preparing a bispecific antibody comprising a variable light chain that has 100% amino acid sequence identity to a variable light chain specific for a first antibody and a variable light chain domain specific for a second antibody. Claims 94-101 are directed to method of preparing a bispecific antibody comprising a first and a second variable light chain polypeptide, wherein each of the first and second variable light chain polypeptides has 3 CDRs and has at least 98% amino acid sequence identity to the other variable light chain polypeptide, and the first and second variable light chain polypeptides differ only at amino acid positions outside of the CDRs. Claims 102-109 are directed to a method of preparing a bispecific antibody that comprises a variable light chain, wherein the variable light chain has at least 98% amino acid sequence identity to a first antibody variable light chain domain specific for a first antigen and to a second antibody variable light chain domain specific for a second antigen or both, wherein the variable light chain polypeptide

and first and/or second antibody variable light chain domain differ from one another only at amino acid positions outside of CDRs.

Applicants submit that the cited references, alone or in any combination, do not teach methods of preparing a bispecific antibody as claimed.

1. The references when combined do not teach all of the elements of the claimed invention.

Applicants submit that even when all of the references are combined, they do not disclose all of the elements of the claimed invention. As stated above, the present claims provide for a method for making a bispecific antibody comprising light variable domains that have at least 98% amino acid sequence identity. The Applicants have discovered and disclosed that light chains comprising at least 98% amino acid sequence identity can likely be found for any V_L comparison of antibodies directed against different antigens (Table 6). Such light chains allow for methods of preparing bispecific antibodies with greater efficiency by eliminating the mispairing of light and heavy chains.

None of the cited references, alone or in combination, teach a method of making a bispecific antibody comprising light chain variable domains that have at least 98% amino acid sequence identity.

Reddy et al. teaches a method of producing a BsMAb recognizing both CEA and doxorubicin for site-specific drug delivery. The method involves fusing myeloma cells each producing an antibody of different specificity. This reference does not discuss any problems with the formation of the bispecific antibodies and is not concerned with the pairing of light and heavy chains. Reddy et al. does not teach or suggest a method of forming bispecific antibodies with a common variable light chain, or variable light chains that have at least 98% amino acid sequence identity to one another and that differ only in amino acid positions outside of CDRs. Reddy et al. does not further suggest producing a bispecific antibody by culturing a host cell comprising one or more nucleic acids encoding a first polypeptide, the second polypeptide and the variable light chain polypeptide or one or more nucleic acids encoding a first and second variable light chain

polypeptide that have at least 98% amino acid sequence identity to one another and differ at amino acid positions outside of CDRs.

The Vaughan et al. reference discloses and is directed to an scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not teach or suggest that such light chains should be used over other light chains or that these light chains can or should be used in bispecific antibodies. In addition, Vaughan et al. does not describe or suggest forming a bispecific antibody by using variable light chains that have at least 98% amino acid sequence identity to one another and differ only in amino acid positions outside of CDRs or forming a bispecific antibody comprising a first and second binding domain with the same light chain. Since this reference does not teach or suggest a method of preparing bispecific antibodies, the reference does not teach or suggest using light chains having at least 98% amino acid sequence identity or even 100% amino acid sequence identity over other light chains to prepare a bispecific antibody in high yield. Thus, the Vaughan et al. reference also fails to disclose culturing a host cell that comprises one or more nucleic acids encoding a first polypeptide, a second polypeptide and the light chain variable domain polypeptide.

Moreover, Applicants submit that one of skill in the art would not be motivated to make an anti-CEA and anti-doxorubicin bispecific antibody using the antibodies of Vaughan because these antibody light chains have different sequences in the CDR L3 as shown in Table 2. Although Table 2 indicates that these antibodies use the same germline sequence and V_L segment, the CDRH3 sequences differ. The reference also states that during the formation of the antibody library all of the selected V genes, except Vλ3 DPL16 of DEA-5 and Oe-2G4 contained amino acid differences from the corresponding germline segment; indicating they contain PCR errors and/or somatic mutations. Some of the antibodies are more extensively mutated from the germline than others. See page 310, last page to page 311, first paragraph. In addition, Cox et al. and Williams et al. references show that even though an antibody or antigen binding fragment may have the same germline Vλ segment, the variable domain can have different

sequences. Thus, Applicants submit that even if the argument could be made that one of skill in the art would be motivated to use antibody sequences as disclosed by Vaughan, they would not utilize any of the methods as claimed by Applicants.

Nor does the Zhu et al. reference remedy these deficiencies. This reference is directed to the use of domain interface engineering strategies to enhance the preference of a pair of single chain Fv proteins to form heterodimers rather than homodimers. Zhu et al. nowhere discuss, however, any problems with the pairing of light and heavy chains. Zhu et al. reference does not teach or suggest a method of forming bispecific antibodies comprising variable light chains that have at least 98% amino acid sequence identity to one another and differ only in amino acid positions outside of CDRs.

Therefore, Applicants submit that none of the references, alone or in any combination, disclose all of the elements of Applicants' claims. The Examiner contends, however, that the Applicants have merely "recognized another advantage which would flow naturally from following the suggestion of the prior art," which "cannot be the basis for patentability when the differences would otherwise be obvious." Applicants respectfully disagree.

Applicants have not in fact merely recognized an advantage that flows naturally from the prior art, because the prior art, even if combined, does not result in a method of preparing bispecific antibodies comprising light chains as claimed. As discussed above, none of the references, alone or in combination, recognizes that light chains as claimed can likely be found for any V_L comparison. Nor do any of the references even teach or suggest the existence of a problem with the mispairing of light and heavy chains, let alone teach or suggest any solution to such a problem. It is the Applicants who have identified a solution to the problem of chain mispairing. Consequently, the present claims are patentable over the cited references, alone or in any combination, for the foregoing reasons.

2. <u>The Examiner has not established a motivation to combine the cited references in the suggested manner.</u>

"A rejection cannot be predicated on the mere identification . . . of individual

components of the claimed invention. Rather, particular findings must be made as to the reason the skilled artisan, with no known knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Ecolochem Inc. v. Southern Calif. Edison Co.*, 227 F3d 1361, 1375 (Fed. Cir. 2000). "Obvious to try" is not the standard. *Id.* at 1374.

Applicants submit that one of skill in the art would not be motivated to combine or modify the references as cited by the Examiner. As discussed previously, the Reddy et al. reference is directed to showing the functionality and dual specificity of specific bispecific antibodies. This reference discloses the preparation of a rodent bispecific antibody against CEA and doxorubicin for therapeutic use. The Examiner contends that one of skill reading Reddy et al. would be motivated to produce a high-affinity human bispecific antibody against CEA and doxorubicin comprising a light chain disclosed by Vaughan et al., because Vaughan et al. teaches a first human antibody fragment that binds doxorubicin, and a second antibody fragment that binds CEA. Applicants respectfully disagree.

There is no discussion in Reddy et al. of any problems with making or using the antibody disclosed therein, or any other bispecific antibody. This reference does not teach or suggest a bispecific antibody comprising variable light chains that have at least 98% amino acid sequence identity to one another and differ only at amino acid positions outside of CDRs as a solution to preparing and/or increasing yield of bispecific antibodies. Moreover, it is unclear how human or humanized antibodies could be produced using the hybridoma method of Reddy et al.

Vaughan et al. is also not directed to methods of preparing bispecific antibodies. The Vaughan et al. reference is directed to forming a *diverse* scFv phage library of naïve antibody variable domains. This reference does not describe bispecific antibodies or any concerns regarding the methods for producing bispecific antibodies. Nor does this reference teach or suggest use of the disclosed variable light chains in a bispecific antibody. Moreover, as discussed previously, even if it could be argued that one of skill in the art would be motivated to use the sequences of Vaughan et al. to make a bispecific antibody, they still would not be practicing the methods as claimed. Thus, this reference

does not teach or suggest that light chains that have at least 98% amino acid sequence identity or even 100% amino acid sequence identity can be used to improve yield of bispecific antibodies.

Therefore, one of skill in the art would simply not be motivated to modify the teachings of Reddy et al. to prepare a bispecific antibody against CEA and doxorubicin comprising light chains disclosed by Vaughn et al, because neither of the references teaches or suggests an advantage to, or desirability of, making such a combination. Moreover, the references are each directed to different methods- the Vaughan et al reference is directed to generating a library for phage display and the Reddy reference is directed to a method of making a bispecific antibody by fusing myeloma cells. Applicants respectfully submit that the Examiner is employing an improper "obvious to try" rationale to combine the cited references, rather than establishing a motivation or suggestion in the prior art to make the combination.

3. The references do not provide a reasonable expectation of success in obtaining the claimed invention.

As discussed above, the present claims are directed to methods of preparing bispecific antibodies, comprising variable light chains polypeptides having at least 98% amino acid sequence identity or 100% amino acid sequence identity. None of the cited references teach or suggest the feasibility of employing a process including variable light chains having at least 98% amino acid sequence identity in a bispecific antibody against any two given antigens.

The Vaughan et al. reference does not teach or suggest using variable light chain that have 98% amino acid sequence identity or even 100% amino acid sequence identity in a bispecific antibody. Although the Vaughan et al. reference discloses that the same light chain is sometimes paired with different heavy chains, there is no disclosure in Vaughan et al. that a light chain having at least 98% amino acid sequence identity can be found in pairwise combinations of any two antibodies of different specificities. The Zhu et al. reference and the Reddy et al. reference also do not teach or suggest that variable light chain that have at least 98% or even a 100% amino acid sequence identity between

antibodies that have different antigenic specificity occurs to allow for the identification of such variable light chain domain. One of skill in the art reading the cited references would not know that light chains having at least 98% amino acid sequence identity could be identified for any two antigens. Thus, Applicants submit that even if the references are combined they do not provide a reasonable expectation of success.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103 rejection of the claims, because the references when combined do not disclose all of the elements of Applicants' claimed invention, there is no motivation to combine the references cited by the Examiner, and there would be no reasonable expectation of success based on these references a method for preparing a bispecific antibody as claimed.

Requst for Interview

Applicants request an interview with the Examiner and his supervisor upon receipt of these papers. Applicants request that the Examiner call Applicant's representative to schedule such an interview.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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